

Somehow...It's Always Lupus

Shannon Rickner, MD; Lewis S. Nelson, MD

A 14-year-old girl presented with normal mental status following an intentional overdose. Within 30 minutes of arrival, she developed profound hypotension, electrocardiogram abnormalities, and hypokalemia.

Case

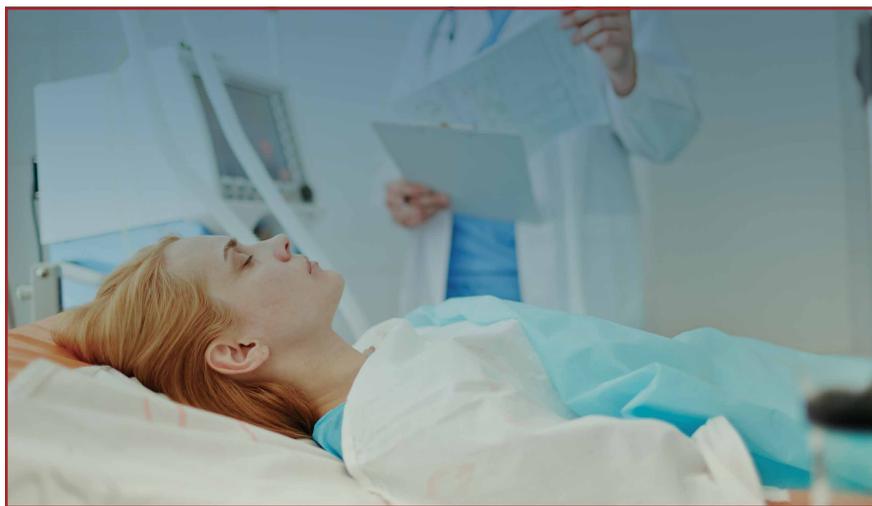
A 14-year-old girl with no known medical history presented to the ED via emergency medical services (EMS) approximately 1.5 hours after intentionally ingesting what she described as “a handful or two” of her mother’s lupus prescription medication in a suicide attempt. Initial vital signs and physical examination were normal, and her only complaint was nausea.

Thirty minutes after presentation, the patient suffered acute cardiovascular (CV) collapse: blood pressure, 57/39 mm Hg; heart rate, 90 beats/min. An initial electrocardiogram (ECG) revealed QRS duration of 123 milliseconds and QTc duration of 510 milliseconds, along with nonspecific T-wave abnormalities. A 150-mEq intravenous (IV) bolus of sodium bicarbonate and a 40-mEq potassium chloride IV infusion were administered, and both epinephrine and norepinephrine IV infusions were also initiated. A basic metabolic panel obtained prior to

medication administration showed a potassium concentration of 1.9 mmol/L.

What is the differential diagnosis of toxicological hypokalemia?

Hypokalemia may be reflective of diminished whole body potassium stores or a transient alteration of intravascular potassium concentrations. In acute ingestions and overdose, the etiology of the hypokalemia



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Dr Rickner is a senior medical toxicology fellow and an assistant clinical instructor, department of emergency medicine, University of Texas, Southwestern and Parkland Health and Hospital System, Dallas. **Dr Nelson**, editor of “Case Studies in Toxicology,” is professor and chair of the department of emergency medicine, Rutgers New Jersey Medical School; and a medical toxicologist, New Jersey Poison Information & Education System, both in Newark, New Jersey. He is also associate editor, toxicology, of the EMERGENCY MEDICINE editorial board.

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is often electrolyte redistribution through either blockade of constitutive outward potassium leakage (eg, barium, insulin, quinine) or through increased activity of the Na⁺/K⁺-ATPase pump (eg, catecholamines, insulin, methylxanthines). This activity has little effect on whole body potassium stores, but can result in a profound fall in the serum potassium. While mild hypokalemia is generally well tolerated, more severe potassium abnormalities can cause muscular weakness, areflexic paralysis, respiratory failure, and life-threatening dysrhythmias. Common ECG findings include decreased T-wave amplitudes, ST-segment depression, and the presence or amplification of U waves.

Case Continuation

While the emergency physicians were stabilizing the patient, her mother provided additional information. Approximately 30 minutes after the exposure, the patient had become nauseated and told her mother what she had done. Her mother called EMS, and the patient was transported to the hospital, where she rapidly became symptomatic. Despite CV decompensation, she remained neurologically intact. On further questioning, the patient admitted to ingesting 6 g of her mother's prescription of hydroxychloroquine (HCQ) in a suicide attempt but denied taking any other medications. She was stabilized on vasopressors and admitted to the intensive care unit.

What characterizes hydroxychloroquine toxicity?

Hydroxychloroquine is an aminoquinoline antibiotic that is classically used as an antimalarial to treat infection with *Plasmodium vivax*, *P ovale*, *P malariae*, and susceptible strains of *P falciparum*. In the United States, it is more commonly used to manage both rheumatoid arthritis and systemic lupus erythematosus (SLE), debilitating diseases which are estimated to affect anywhere from 161,000 to 322,000 Americans.¹ Hydroxychloroquine is con-

sidered first-line therapy for SLE, but its mechanism of action in treating SLE-associated arthralgias is unclear.

Hydroxychloroquine is structurally similar to quinine and chloroquine (CQ), and not surprisingly exerts quinidine-like effects on the CV system with resultant negative inotropy and vasodilation. Its toxicity is characterized by rapid onset of clinical effects including central nervous system depression, seizures, apnea, hypotension, and arrhythmia. After large overdoses, cardiac arrest and death can occur within hours.

Hypokalemia is another hallmark of HCQ toxicity. It is thought to develop secondary to potassium channel blockade, which slows the constitutive release of potassium from the myocytes.² As noted, the hypokalemia is transient and does not reflect whole-body depletion. With CQ, which is considered more toxic, there appears to be a correlation between the quantity of CQ ingested and both the degree of hypokalemia and the severity of the outcome. It is reasonable to assume the same for HCQ. There are little data to support that hypokalemia itself causes cardiotoxicity in patients with CQ or HCQ overdose.

Although lethal doses are not well established, animal studies suggest that HCQ is much less toxic than CQ, for which the clinical toxicity is better understood due to its more widespread use in overdose abroad.³ In children, the reported therapeutic dose is 10 mg/kg, but the minimum reported lethal dose was a single 300-mg tablet (30 mg/kg in a toddler). In adults, the toxic dose is reported as 20 mg/kg with lethal doses suggested to be as low as 30 mg/kg.

What are the treatment modalities for patients with hydroxychloroquine toxicity?

By analogy with the treatment of CQ poisoning, the mainstay of HCQ therapy is supportive care, including early intubation and ventilation to minimize metabolic demand. Direct-acting inotropes and vasopressors should be administered

after saline to treat hypotension. Because of its large volume of distribution, extracorporeal removal has not proved to be of clinical value.^{4,5} Though data are sparse to determine its efficacy, there may be a role for giving activated charcoal, particularly following large overdoses—if it is given early after exposure and the patient has normal consciousness. If the patient is intubated and aspiration risk is minimized, gastric lavage may also be beneficial—especially when performed within an hour of the overdose. Syrup of ipecac should not be used.

High-dose diazepam is typically recommended, again by analogy with CQ, although there is no clear mechanism of action and its use remains controversial. Its protective effect in patients with CQ overdose is based on swine and rat models that demonstrated dose dependent relationships between diazepam and survival.^{6,7} A prospective study of CQ toxicity in humans reported improved survival rates when high-dose diazepam was given in combination with epinephrine.⁸ However, this study is limited by its comparison of prospectively studied patients with a retrospective control. A subsequent prospective study of moderately CQ-intoxicated patients did not find a benefit from treatment with diazepam.⁹ Furthermore, it remains unclear if the proposed benefit from high-dose diazepam in CQ toxicity may be extrapolated to HCQ, and cases of even massive HCQ ingestions report good outcomes without the use of high-dose diazepam.¹⁰

How aggressively should hypokalemia in hydroxychloroquine toxicity be treated?

As noted earlier, hypokalemia resulting from HCQ toxicity is transient, and aggressive repletion may result in rebound hyperkalemia once toxicity resolves. However, these dangers should be balanced with risks of hypokalemia-induced ventricular arrhythmias. Additionally, hypokalemia may be worsened by sodium bicarbonate that is administered to correct

QRS prolongations, increasing the risk of dysrhythmia. Correction of hypokalemia in these cases is necessary but should be done with care and monitoring of serum potassium concentrations to minimize risk of hyperkalemia-induced ventricular arrhythmia.¹¹

Case Conclusion

Throughout treatment, the patient remained neurologically intact. She did not receive benzodiazepines. The epinephrine and norepinephrine infusions were weaned, and she was discharged on hospital day 3 with no neurological or cardiac sequelae. She received an inpatient psychiatric evaluation and was referred to outpatient services for ongoing care.

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